REMARKS

With entry of this amendment, claims 55-75 and 77-92 are pending. The claims have been amended to address the objections and 35 USC § 112 rejections and not to distinguish from the prior art. Support for the amended claims can be found in the originally filed claims and throughout the specification. No new matter has been added. Reconsideration is requested.

Applicants acknowledge the duty of disclosure under Rule 56, as noted by the Examiner.

The references to the figures throughout the specification have been amended as required by the Examiner to conform to the drawing corrections which were indicated to be necessary.

Claims 57-65, 69-77 and 79-83 were objected to under 37 CFR 1.75(c) as being in improper form because of improper multiple dependencies. The subject claims have been amended or rewritten and are believed to be free of the objection.

Claims 54-56, 66-68 and 78 were rejected under 35 USC § 112, second paragraph as being indefinite. Claims 55-56 and 68 were indicated to be indefinite because they depended from cancelled claims. The subject claims have been amended to recite the correct dependency.

Claims 54-56, 66-68 and 78 were considered by the Examiner to be indefinite in the recitation of "and/or". Although Applicants do not agree with the Examiner's position,

in order to expedite prosecution this expression has been removed from the amended claims.

Claim 54 was considered to contain an improper Markush Group. The Markush Group at issue is presently recited in claim 85, and is submitted to be in proper form. Claim 54 was also considered to be indefinite in the recitation "selected from the cytokine superfamily". This limitation is presently found in claims 86 and 87, which are believed to be free of the rejection.

Claim 56 was considered to be indefinite in the recitation "for example". This expression has been deleted from the claim and the examples are now present as limitations in new claim 89.

Claims 66-68 were considered to be indefinite in the recitation "in close proximity". This expression has been removed from the amended claims.

Claim 66 was considered to be vague and indefinite in the recitation "a partial or complete catalytic center". The claim has been amended to remove this expression.

Claim 78 has been rejected under 35 USC § 112, first paragraph, as not being enabled. It is the Examiner's position that the specification does not provide sufficient evidence to establish that the claimed method would indeed cure HIV. Applicants note that claim 78 has been amended to recite "obtaining at least inhibition or suppression" of HIV.

Applicants respectfully submit that the claim is enabled by the present specification for the reasons detailed below.

The Examiner has acknowledged on page 9, lines 31-32 of the Office Action that methods of removing antibodies by plasmaphoresis were well known in the art at the time of filing of the present application. Thus, there would have been no bar to a skilled artisan carrying out such a process and that aspect of the invention is fully enabled. A number of other technologies for antibody removal have been disclosed in the specification which can be routinely carried out by those of skill in the art.

The present specification provides illustration of actual success using the method on pages 20-21. The specification illustrates that the presence of HIV-IIIB can lead to a persisting infection in a fully active human immune system under in vivo conditions provided antibodies are present. It is also illustrates that the absence of antibodies leads to a quick termination of a persistant infection in the in vivo setting, presumably occuring by T-cells. Applicants respectfully submit that this evidence overcomes the objections detailed by the Examiner in the first paragraph on page 5 of the Office Action.

Claims 66-68 have been rejected under 35 USC § 102(b) as being anticipated by any one of Smit et al., Lopez et al., Lokker et al., or Shaw et al. It is the Examiner's position that each of these references teaches modifications to

proteins, in particular to interleukins. This rejection is respectfully traversed.

None of the cited articles teaches enhanced biological activity, as in the presently claimed invention. More specifically, there is no teaching of antagonistic activity. Furthermore, there is no teaching of a modification in the catalytic center.

Applicants respectfully submit that biological activity is attributable both to the catalytic activity and to the reeptor binding capacity. Where receptor binding capacity has been reduced or enhanced, the catalytic center need not have been altered in any way to produce a modification in biological activity. Thus, any suggestion of altered biological activity due to a modification disclosed in the prior art does not automatically mean that the modification must have been associated with the catalytic center or be in the catalytic center itself. Furthermore, there is no association whatsoever in the cited documents of a metal binding center being involved in the modifications or in altered biological activity.

It is submitted that the Shaw reference has nothing whatsoever to do with altered biological activity, but deals with the generation of homogenously modified substances. There is no disclosure therein which would aid the skilled artisan in addressing the problem of enhancing biological activity, specifically antagonistic activity.

With respect to the Lopez reference, Applicants first point out that the method of determining enhanced biological activity is not in accordance with generally accepted methods in the art. Concentrations of partially purified modified substances (in mixtures containing many other proteins) are determined by ELISA or by gel scanning densitometry after Coommassie staining. Conformational chanes as a result of modifications can have a profound effect on both methods. As the compounds have only been partially purified, it cannot be excluded that profound conformational changes have taken place. The specific change of Asp 101 to Ala 101 mentioned in the documentcould quite likely have resulted in disruption of ionic interactions in the modified protein versus the unmodified protein. Furthermore, it cannot be excluded that the expression of the modified substance resulted in some unpredictable type of different folding pattern. The consequence of these factors is that the estimated concentraion may be too low and the specific activity be overestimated. Applicants respectfully submit that for the above reasons, the conclusion of enhanced activity is not supported.

With respect to Lokker, Applicants note that this reference only used ELISA detection on partially purified mixtures and thus has problems which are analogous to Shaw. Furthermore, only one means of determination was used in the Lokker document.

None of the cited documents demonstrate the generation of proteins for which enhanced activity has been achieved. This is in contrast to the method according to the present invention, where the process of gradual modification ensures the protein concentration is easily determined as it does not change. In addition, in the method described in the present specificaion, the real conformational changes can easily be detected due to the absence of other contaminating proteins. In contrast, the molecular biology modification route suggested in the prior art leads to purification problems, and the prior art clearly shows only partially purified proteins. Characterization of such partially purified proteins is not possible, and consequently the ascertainment of structure-function relationships is not possible.

For all of the above reasons, Applicants submit that the presently claimed invention is not anticipated by Smit et al., Lopez et al., Lokker et al., or Shaw et al. Withdrawal of the rejection is respectfully requested.

Claims 54-56 and 66-68 have been rejected in view of Smit et al., Lopez et al., Lokker et al., and Shaw et al. in combination with alleged admissions in the present specification at page 15, lines 1-19. This rejection is respectfully traversed.

In addition to the failure of the above-referenced documents to teach or suggest the presently claimed invention, Applicants submit that there is nothing disclosed in the

present specification which can be combined with those documents to yield the invention. Although the use of endoproteases as such and the use of quantitative mass spectrometry were well known standard techniques, there was never a previous disclosure or suggestion of the use thereof in a process as described and claimed in the present application. The present invention could only occur when a sufficient signal to noise ratio and resolution was attained to allow a quantitative detection and screening of all fragments in both the modified and unmodified form. The knowledge of these standard techniques in no way suggested or enabled the present invention. Withdrawal of the rejection is respectfully requested.

Claim 78 has been rejected under 35 USC § 103 as being unpatentable over Robinson et al. (The Lancet). This rejection is traversed for the following reasons.

The Lancet article was published in 1988, six years prior to the filing of the present application. The Examiner has stated that current insight is that reducing antibody titres to HIV is not expected to have a good effect, but on the contrary, is expected to worsen the situation (page 4, lines 30-32). This contradicts the Examiner's later assertion that a skilled artisan would be motivated to remove antibody with a view of combatting viral infection with a reasonable expectation of success.

Applicants strongly disagree with the Examiner's assertion that the teaching at the time of filing of the present application was that reduction in antibody would effectively treat HIV infection in vivo. On the contrary, a skilled artisan at that time would have expected antibody presence to be effective. Applicants submit that a person skilled in the art reading the Lancet article would have been skeptical about extrapolating tentative in vitro data as being indicative of a reasonable expectation of sucess when treating in vivo HIV infection.

Applicants submit that the teaching of the Lancet article should in no way be considered to be that antibody removal is a means for achieving a cure of HIV infection. First, no in vivo data is presented. Second, the data shown merely demonstrates that complement in combination with the presence of antibody in vitro is responsible for enhanced viral activity. The tests carried out in the presence of antibody without complement and complement without antibody were also performed in vitro. From the results it could be inferred that removal of either of the two components had an in vitro effect--i.e. that the enhanced activity revealed for the combination was no longer noted. It cannot be concluded that removal of antibody would result in inhibition or suppression of viral infection.

In conclusion, the data disclosed in the Lancet reference would not have lead a skilled artisan to the conclusion that

removal of antibody would have been effective treatment for HIV infection, particularly in light of the assessment made by the Examiner of the state of the art on page 5 of the Action. The generally accepted view of persons of skill in the art at that time was that reducing antibodies against the virus would not inhibit or suppress infection, but on the contrary, would be contraindicated.

For all of the above reasons, withdrawal of the § 103 rejection of claim 78 is respectfully requested.

All objections and rejections having been addressed, it is submitted that the application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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